Title of the Invention

The title of the invention has been amended to more specifically correspond to the claimed subject matter.

Restriction Requirement

The Examiner's withdrawal of the restriction requirement is acknowledged with appreciation.

Rejection of Claims 11, 14, 15, 33, 36 and 37 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 11, 14, 15, 33, 36 and 37 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner states that the recitation "competitively inhibits binding of TNFα to monoclonal antibody cA2" is considered new matter since support for it is not found in the specification. Applicants disagree with this assessment.

Support for the phrase "competitively inhibits binding of TNFα to monoclonal antibody cA2" is found in the specification, for example, at page 12, lines 7-10.

Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection of Claims 9-10, 12-15, 31-32 and 34-37 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has maintained several of the rejections of Claims 9-10, 12-15, 31-32 and 34-37 under 35 U.S.C. § 112, second paragraph. Certain claims have been amended in response to the rejection. As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. A discussion of each of the specific rejections made by the Examiner follows:

a) The Examiner maintains that Claims 9, 12-15, 31 and 34-37 are vague and indefinite in the recitation of "chimeric" because "all of the definitions provided in the specification are open ended, thus not setting the metes and bounds of a 'chimeric antibody'". Applicants respectfully disagree with this assessment. However, in an effort to advance prosecution in the subject application, Claims 9 and 31 have been amended to delete the phrase "chimeric antibody". In addition, as suggested by the Examiner, Claims 12 and 34 have been amended to recite that the chimeric antibody comprises a non-human variable region specific for TNF or an antigen-binding portion thereof and a human constant region. Support for this amendment is found in the specification, for example, at page 11, lines 16-20. It is noted that Claims 13-15 depend from Claim 12 and Claims 35-37 depend from Claim 31. As amended, Claims 9, 12-15, 31 and 34-37 even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention, thereby obviating this rejection under 35 U.S.C. § 112, second paragraph.

b) Claims 10, 13, 32 and 35 have been rejected as vague and indefinite in the recitation "binds to one or more epitopes" because by "art accepted definition, a single antibody binds to one epitope" and thus, "it is unclear how the claimed antibody can bind to one or more epitopes". Applicants respectfully disagree with this assessment.

An antigen can have more than one copy of a particular epitope. Thus, unless inhibited by steric constraints, a single antibody can bind to more than one epitope. See Abbas *et al.*, *Cellular and Molecular Immunology*, 3rd ed., Philadelphia: W.B. Saunders Co., p. 54 (1997); attached hereto as Exhibit A. Thus, it is clear how the claimed antibody can bind to one or more epitopes. This can be true where, as here, the antigen is a multimer (TNFα is a trimer). A person skilled in the art would find the phrase "binds to one or more epitopes" to be definite.

Notwithstanding the above, Claims 10, 13, 32 and 35 have been amended to delete the phrase "one or more epitopes" and recite "an epitope". No difference in scope is seen as an antibody which can bind multiple epitopes, can bind each individual epitope.

c) The Examiner maintains that Claims 14-15 and 36-37 are vague and indefinite in the recitation of "cA2" because "it is unclear whether cA2 designates a monoclonal chimeric antibody secreted by a unique cell line or whether it designates any chimerization of the A2 monoclonal antibody." Applicants respectfully disagree with the Examiner's assessment that the term "cA2" is unclear.

As stated in Applicants' specification (see, e.g., page 16, lines 14-15 and 18-19), cA2 designates a chimeric monoclonal antibody which is characterized by the antigen binding variable region of monoclonal antibody A2 and the constant regions of a human IgG1, κ immunoglobulin (see, e.g., page 12, lines 23-26). In addition, significant description of the properties of monoclonal antibody cA2 (e.g., epitopic specificity and affinity) is disclosed in U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272; see, e.g., Examples X-XII therein) and U.S. Application No. 08/324,799 (now U.S. Patent No. 5,698,195; see, e.g., Examples X-XII therein), both incorporated by reference in Applicants' specification (see, e.g., page 12, lines 12-17). Additionally, the sequences of the antibody are described therein. Thus, the term "cA2" is clear and definite, when read in light of Applicants' specification. Withdrawal and reconsideration of this rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Rejection of Claims 11, 14, 15, 33, 36 and 37 Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of Claims 11, 14, 15, 33, 36 and 37 under 35 U.S.C. § 112, first paragraph, alleging that there is an inadequate written description of the

invention and a nonenabling disclosure without complete evidence either that the cell lines expressing A2 and cA2 antibodies are known and readily available to the public or complete evidence of the deposit of the biological materials is maintained. The Examiner states that:

> Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. . . . Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas.

Applicants respectfully disagree with the Examiner's conclusion.

Claims 14, 15, 36 and 37 recite the monoclonal antibody cA2. Claims 11 and 33 have been cancelled.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. Exact reproducibility is not required for enablement under 35 U.S.C. § 112, first paragraph. Staehelin v. Secher, 24 U.S.P.Q.2d 1513, 1518 (Bd. Pat. App. Int. 1992). The Court of Appeals for the Federal Circuit has stated that:

> No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.

In re Wands, 8 U.S.P.Q.2d 1400, 1403 (Fed. Cir. 1988). See also M.P.E.P. § 2404.02.

The court also stated in Wands, where a similar rejection was reversed:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. Id. at 1406.

The court in Wands found that screening hundreds of hybridoma clones for a specific antibody did not involve undue experimentation. That is, the court in Wands found that the process of screening hybridomas to select those having the desired property was straightforward with a very high likelihood of success.

In essence, the present situation is closely analogous to the facts in Wands. The specification provides considerable direction and guidance and working examples on how to produce and identify chimeric anti-TNF antibodies which would be chemically and structurally similar to those claimed. See the specification, for example, at page 12, lines 12-17, which incorporates by reference information on cA2 to other U.S. patent applications not listed as priority documents (e.g., U.S. Application No. 08/192,093 (filed February 4, 1994), U.S. Application No. 08/192,102 (filed February 4, 1994; now U.S. No. Patent No. 5,656,272; attached hereto as Exhibit B), U.S. Application No. 08/192,861 (filed February 4, 1994) and U.S. Application No. 08/324,799 (filed October 18, 1994; now U.S. Patent No. 5,698,195; attached hereto as Exhibit C)). U.S. Patent No. 5,656,272 and U.S. Patent No. 5,698,195, for example, disclose detailed methods of producing and identifying monoclonal antibodies which would be chemically and structurally similar to those claimed (see U.S. Patent No. 5,656,272, e.g., col. 15, l. 66 to col. 20, l. 46, col. 26, l. 1 to col. 30, l. 47, and Examples I to X; and U.S. Patent No. 5,698,195, e.g., col. 16, l. 18 to col. 20, l. 67, col. 26, l. 31 to col. 31, l. 15, Examples I to X). Indeed, the Examiner agrees that the specification discloses a method for selecting hybridoma cell lines and monoclonal antibodies for use in the claimed invention.

Thus, given the guidance presented in the specification, antibodies which would be chemically and structurally similar to those claimed can be produced and identified through routine screening. Therefore, it would not require undue experimentation for one skilled in the art to produce and select antibodies for use in the claimed invention.

The Examiner also states in the rejection that:

> the sequence of the entire immunoglobulin would satisfy this enablement requirement. However, partial sequences do not provide adequate enablement, as the claims are drawn to an intact antibody molecule.

Applicants respectfully disagree with this conclusion.

As stated above, Applicants disclose in the specification that monoclonal antibody cA2 consists of the antigen binding variable region of monoclonal antibody A2 and the constant regions of a human IgG1 κ immunoglobulin (see, e.g., page 12, lines 23-26).

The specification incorporates by reference, for example, at page 12, lines 12-17, the nucleic acid and amino acid sequences of the cA2 light chain variable region and the cA2 heavy chain variable region to other U.S. patent applications not listed as priority documents. U.S. Patent No. 5,656,272 (attached as Exhibit B) and U.S. Patent No. 5,698,195 (attached as Exhibit C), for example, disclose the nucleic acid and amino acid sequences of the cA2 light chain variable region in Figure 16A and the cA2 heavy chain variable region in Figure 16B. The constant regions of a human IgG1 κ immunoglobulin are readily available in the art. Thus, it would be straightforward for one skilled in the art to produce a monoclonal antibody corresponding to the cA2 antibody, given the guidance presented in the specification (the sequences for the cA2 light and heavy chain variable regions) and what was known to the skilled artisan at the time the subject application was filed (the constant regions of a human IgG1 κ immunoglobulin). The PTO has not provided evidence or reasoning which would support a contrary conclusion. That is, there is no

basis to question that the skilled artisan, armed with the sequences for the cA2 light and heavy chain variable regions, could produce a monoclonal antibody corresponding to the cA2 antibody.

In view of the foregoing discussion, withdrawal and reconsideration of this rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection of Claims 6, 8-15 and 29-37 Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of Claims 6, 8-15 and 29-37 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not provide an adequate written description of the invention or enable the scope of the claims. Each specific rejection is addressed in the order presented by the Examiner:

a) The Examiner has maintained the rejection of Claims 6 and 29 on the grounds that it would require undue experimentation for one skilled in the art to practice the claimed invention using the many classes of molecules defined to be a TNF antagonist. The Examiner states that:

> Guidance for making and using of this very broad collection of molecules can not be drawn from the making and using of antibodies in the claimed method.

Applicants respectfully disagree with this conclusion.

The specification teaches that thrombosis can be treated or prevented in an individual by administering a TNF antagonist to the individual in therapeutically effective amounts (see, e.g., page 6, lines 19-20). Examples of TNF antagonists that can be used in the claimed invention are provided in the specification, for example, at page 7, line 9 to page 29, line 7. Numerous TNF antagonists are also known in the art. As the Examiner states, the specification exemplifies methods that comprise

administration of anti-TNF antibodies (see Paper No. 8, page 7). Since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen (in this case TNF), it is expected, based upon scientific reasoning, that the claimed invention works in the same manner using other TNF antagonists. The particular route by which TNF activity is inhibited, blocked, abrogated or interfered with is not critical. One skilled in the art would reasonably expect that the invention would work similarly with other members of the genus. That is, one skilled in the art would accept the assertions in the specification as true and enabling. No evidence to the contrary has been presented, only unsupported conclusions.

Thus, armed with Applicants' teachings, it would not require undue experimentation for one skilled in the art to practice the claimed invention with a reasonable expectation of success.

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

b) Claims 6, 8 and 29-30 are rejected on the grounds that they "are broad enough to read on the administration of murine antibodies." The Examiner states that:

> U.S. Patent 5,698,195 (col. 3, line 37-40) notes the ineffectiveness of murine antibodies as in vivo therapeutic agents in humans. Thus, one of skill in the art could not practice the claimed invention commensurate with the scope of the claims with a reasonable expectation of success.

Applicants disagree with this assessment.

The cited patent, at column 3, lines 36-37, discloses that "experience with anti-TNF murine mAb therapy in humans has been limited." At column 3, lines 37-45, the results of a phase I study in which seven of fourteen patients with severe septic shock developed a human anti-murine antibody response after treatment with a murine anti-TNF mAb are described. Although it is stated that the treatment suffers from known problems due to

immunogenicity from the use of murine heavy and light chain portions of the antibody (col. 3, l. 42-45), and that such immunogenicity causes decreased effectiveness of continued administration and can render treatment ineffective in patients undergoing diagnostic or therapeutic administration of murine anti-TNF antibodies (col. 3, l. 45-48), this does not support a conclusion that murine anti-TNF antibodies would be expected to be ineffective in the claimed methods.

Thus, for the reasons discussed above, it would not require undue experimentation for one skilled in the art to practice the claimed invention, commensurate with the scope of the claims, with a reasonable expectation of success, given the guidance presented in the specification.

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

c) The Examiner has rejected Claims 6, 8-15 and 29-37 on the grounds that "it is unpredictable that one of skill in the art could practice the claimed invention commensurate with the scope of the claims with a reasonable expectation of success and without undue experimentation." The Examiner states that:

> Active rheumatoid arthritis is a distinct disease state, with unique pathological parameters that are known to be associated with the increased production of TNF . . . Such results obtained with the administration of anti-TNF antibodies in rheumatoid arthritis can not be generalized to all types of thrombosis, where TNF production does not necessarily play a role in pathology.

Applicants respectfully disagree with the Examiner's conclusion that one skilled in the art could not practice the claimed invention with a reasonable expectation of success and without undue experimentation given the guidance provided in the specification.

To be enabling under 35 U.S.C. § 112, first paragraph, the specification of a patent must teach those skilled in the art how

to make and use the full scope of the claimed invention without undue experimentation. The Court of Appeals for the Federal Circuit has stated that "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." Id.

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. Id.

The specification teaches that thrombosis can be treated or prevented in an individual by administering a TNF antagonist to the individual in therapeutically effective amounts (see, e.g., page 6, lines 19-20). Examples of TNF antagonists that can be used in the claimed invention are provided in the specification, for example, at page 7, line 9 to page 29, line 7. Guidelines for route of administration and dosages are provided in the specification, for example, at page 29, line 9 to page 32, line 4.

The Examiner acknowledges that the specification demonstrates that the administration of anti-TNFα antibodies to rheumatoid arthritis patients results in a decrease in elevated fibrinogen levels to a range closer to normal and that inhibition of the biological activity of TNFα reduces fibrinogen and platelet levels in individuals with active rheumatoid arthritis. Since platelets and fibrinogen play integral roles in thrombosis, this evidence would satisfy one skilled in the art on the effective filing date of the application that anti-TNF antibodies would likely be effective in the treatment of thrombosis. That is, one skilled in the art would reasonably expect that a means of decreasing fibrinogen levels would likely be effective in the

treatment of thrombosis. No evidence to the contrary has been presented.

In addition, since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen (in this case TNFα), it is expected, based upon scientific reasoning, that the claimed methods work in the same manner using other TNFα antagonists.

It is agreed that rheumatoid arthritis is a distinct disease, with unique pathological parameters that are known to be associated with an increased production of TNF. This, however, does not lead to the conclusion that a means of decreasing a component which plays an integral role in thrombosis, i.e., fibrinogen levels, would not be effective in the treatment of the disease.

With regard to Claims 29-37, the Examiner additionally states that "[t]here is no evidence of record that individuals with active rheumatoid arthritis are suffering from or at risk of thrombosis." Applicants do not understand the relevance of this conclusion.

It is noted that the specification discloses at page 4 that many patients with rheumatoid arthritis ultimately die from cardiovascular and cerebrovascular diseases (see page 4, lines 2-4). The specification also discloses that persistently elevated plasma fibrinogen and/or platelet levels are major contributors to the excess cardiovascular and cerebrovascular mortality seen in RA patients (see page 4, lines 4-9). See also Wolfe *et al.*, *Arthritis Rheum.*, 37:481-494 (1994); reference AT on Form-PTO 1449. Thus, based on these teachings of the specification, one of skill in the art would reasonably conclude that certain individuals with rheumatoid arthritis may be suffering from or at risk of thrombosis. No evidence to the contrary has been presented. In any event, the point is not obviously relevant. The invention does not relate to treating RA patients but is relying upon clinical data which supports the claimed use of the composition to treat a new indication.

For the foregoing reasons, Applicants respectfully submit that the guidance provided in the specification is sufficient to teach the skilled artisan how to practice the claimed invention, commensurate with the scope of the claims, without undue experimentation and with a reasonable expectation of success.

The PTO has not explained why it doubts the truth or accuracy of any statement in the disclosure or provided evidence or reasoning which is inconsistent with the teachings of the disclosure. That is, there is nothing of record which might suggest that the claimed invention is not believable to one of ordinary skill in the art.

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

d) Claims 10, 13, 32 and 35 are rejected on the grounds that since "[i]t is art accepted that one antibody binds to one epitope" "[t]he specification provides no instruction for the preparation of antibodies that bind to more than one epitope." The Examiner concludes that "one of skill in the art could not predictably make and use the claimed antibody." Applicants respectfully disagree with the Examiner's conclusion.

As discussed above, an antigen can have more than one copy of a particular epitope. Thus, unless inhibited by steric constraints, a single antibody can bind to more than one epitope. See Abbas *et al.*, *Cellular and Molecular Immunology*, 3rd ed., Philadelphia: W.B. Saunders Co., p. 54 (1997); attached hereto as Exhibit A. This can be true where, as here, the antigen is a multimer (TNFα is a trimer).

The specification provides methods for producing antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 or about 59-80 of hTNFα. Specifically, the specification provides methods for producing anti-TNF antibodies and for determining the epitopic specificity of these antibodies (see, e.g., page 17, lines 11-18, for example, U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272)).

Thus, given the guidance presented in the specification, it would be a routine matter for one skilled in the art to produce and identify antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 or about 59-80 of hTNFα.

Notwithstanding the above, Claims 10, 13, 32 and 35 have been amended to recite that the antibodies bind to an epitope included in amino acid residues of about 87-108 or about 59-80 of hTNFα. No difference in scope is seen as an antibody which can bind multiple epitopes, can bind each individual epitope.

Rejection of Claims 29-30 Under 35 U.S.C. § 102(b)

Claims 29-30 have been rejected under 35 U.S.C. § 102(b) as being anticipated by van der Poll *et al.*.

The Court of Appeals for the Federal Circuit has stated that "[u]nder 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference." Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986) (citations omitted).

Claims 29-30 relate to methods of decreasing plasma fibrinogen in an individual suffering from or at risk of thrombosis comprising administering an anti-TNF antibody to the individual.

The Examiner states that van der Poll *et al.* disclose "an *in vivo* method of decreasing plasma fibrinogen comprising the administration of an anti-TNF antibody". Respectfully, the Examiner has apparently misunderstood the teachings of the cited, reference.

Van der Poll *et al.* found that endotoxin elicited activation of coagulation, as reflected by increases in prothrombin fragment F1 + 2 and thrombin-antithrombin III complexes (TAT) (Van der Poll *et al.*, e.g., p. 448, col. 1, l. 13-16; Fig. 4; and p. 450, col. 1, l. 38-40). Treatment with an anti-TNF antibody did not affect endotoxin-induced coagulation activation (Van der Poll *et*

al., e.g., p. 446, col.2, l. 6-10 (abstract); p. 448, col. 1, l. 19 to col. 2, l. 4; Fig. 4; and p. 450, col. 1, l. 46-50).

Van der Poll *et al.* also found that endotoxin induced fibrinolytic activation, as reflected by an increase in plasmin-α2-antiplasmin (PAP) complexes (Van der Poll *et al.*, e.g., p. 448, col. 1, l. 16-17; Fig. 4; and p. 450, col. 1, l. 38-41). Treatment with an anti-TNF antibody attenuated the endotoxin-induced activation of the fibrinolytic system (Van der Poll *et al.*, e.g., p. 446, col. 2, l. 10-14 (abstract); p. 448, col. 2, l. 12-15; Fig. 4; and p. 450, col. 1, l. 51-53).

At page 450, van der Poll *et al.* state that "the fact that treatment with anti-TNF MoAb blocks fibrinolysis despite ongoing coagulation activation indicates that inhibition of TNF may promote disseminated intravascular coagulation and deposition of thrombi in the microvasculature" (Van der Poll *et al.*, p. 450, col. 2, l. 16-20). Thus, van der Poll *et al.* disclose that treatment with an anti-TNF antibody may promote disseminated intravascular coagulation and deposition of thrombi in the microvasculature. Thus, van der Poll *et al.* clearly do not disclose that plasma fibrinogen can be decreased in an individual suffering from or at risk of thrombosis by treatment with an anti-TNF antibody. Therefore, Claims 29-30 are not anticipated by van der Poll *et al.*.

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 102(b) are respectfully requested.

Rejection of Claims 31-37 Under 35 U.S.C. § 103(a)

Claims 31-37 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over van der Poll *et al.* in view of WO92/16553. The Examiner states that:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the A2 and cA2 antibodies, as taught in WO92/16553 in the treatment method taught in van der Poll, which utilize an anti-TNF monoclonal antibody. One of ordinary skill in the art would have

> been motivated to do so with a reasonable expectation of success by the teachings of WO92/16553; on the high binding affinity of the A2 antibody (see p. 9, line 29) and the usefulness of chimeric antibodies, such as cA2, in overcoming the "problems of murine antibody immunogenicity" and to "provide reduced immunogenicity and increased neutralization activity" (see p. 7, lines 14-17).

Applicants respectfully disagree with the Examiner's conclusion that the claimed invention was obvious.

A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. Id.

Claims 31-37 relate to a method of decreasing plasma fibrinogen in an individual suffering from or at risk of thrombosis comprising administering an anti-TNF antibody to the individual. Claims 32-37 further characterize the antibody.

As discussed in detail above, van der Poll *et al.* disclose that treatment with an anti-TNF antibody attenuated the endotoxin-induced activation of fibrinolysis but did not affect endotoxin-induced coagulation activation. Van der Poll *et al.* conclude that treatment with an anti-TNF antibody may promote disseminated intravascular coagulation and deposition of thrombi in the microvasculature. Thus, van der Poll *et al.* clearly teach away from the claimed invention.

WO92/16553 teaches both the A2 and cA2 antibodies, and antibodies which recognize an epitope containing amino acid residues 87-108 or 59-80 of hTNFα.

Neither of the cited references, nor their combination, teach or suggest the claimed method of decreasing fibrinogen in an individual, as claimed in Claims 31-37. Accordingly, a *prima*

facie case of obviousness over the references of record has not been presented.

Withdrawal and reconsideration of this rejection under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

Helen Lee

Helen Lee
Attorney for Applicants
Registration No. 39,270
Telephone: (781) 861-6240
Facsimile: (781) 861-9540

Lexington, Massachusetts 02173
Dated: July 6, 1998